‘475 Patent, Lebreton

another embodiment, the suitable alkaline solution is aqueous solutions containing NaOH. The resulting alkaline gel will have a pH above 7.5. The pH of the resulting alkaline gel can have a pH greater than 9, or a pH greater than 10, or a pH greater than 12, or a pH greater than 13.

The next step in the manufacturing process involves the step of crosslinking the hydrated, alkaline NaHA gel with a suitable crosslinking agent. The crosslinking agent may be any agent known to be suitable for crosslinking polysaccharides and their derivatives via their hydroxyl groups. Suitable crosslinking agents include but are not limited to, 1,4-butanediol diglycidyl ether (or 1,4-bis(2,3-epoxypropoxy)butane or 1,4-bisglycidyloxybutane, all of which are commonly known as BDDE), 1,2-bis(2,3-epoxypropoxy)ethylene and 1-(2,3-epoxypropyl)-2,3-epoxycyclohexane. The use of more than one crosslinking agent or a different

excluded from the scope of the pr

aspect of the present disclosure, the

are crosslinked using BDDE.

The step of crosslinking may b

means known to those of ordinary

skilled in the art appreciate how to

crosslinking according to the nature

carry out crosslinking to an optimiz

Degree of crosslinking for purpos

sure is defined as the percent weight

agent to HA-monomeric units withi

of the HA based composition. It is

ratio of HA monomers to crossl

crosslinker).

The degree of crosslinking in th

present compositions is at least abo

20%.

In some embodiments, the de

between about 4% to about 12%. In

degree of crosslinking is less than a

less than about 5%.

In other embodiments, the degree

than 5%, for example, is about 6% t

In some embodiments, the HA component is capable of absorbing at least about one time its weight in water. When neutralized and swollen, the crosslinked HA component and water absorbed by the crosslinked HA component is in a weight ratio of about 1:1. The resulting hydrated HA-based gels have a characteristic of being highly cohesive.

The HA-based gels in accordance with some embodiments of the invention may have sufficient cohesivity such that the gels will not undergo substantial phase separation after centrifugation of the gel at 2000 rd/min for 5 minutes. In another embodiment, the gels have the characteristic of being capable of absorbing at least one time their weight of water and have sufficient cohesivity such that when swollen with water at a gel/water weight ratio of about 1:1, the gels maintain their integrity, for example, when subjected to centrifugation.

The hydrated crosslinked, HA gels may be swollen to obtain the desired cohesivity. This step can be accomplished by neutralizing the crosslinked, hydrated HA gel, for example by adding an aqueous solution containing of an acid, such as HCl. The gels are then swelled in a phosphate buffered saline (PBS) solution for a sufficient time and at a low temperature.

In one embodiment, the resulting swollen gels are highly cohesive with no visible distinct particles, for example, no visibly distinct particles when viewed with the naked eye. In a preferred embodiment, the gels have no visibly distinct particles under a magnification of less than 35×.

The gels are now purified by conventional means such as, dialysis or alcohol precipitation, to recover the crosslinked material, to stabilize the pH of the material and to remove any un-reacted crosslinking agent. Additional water or a slightly alkaline aqueous solution can be added to bring the concentration of the NaHA in the composition to a desired concentration.

The pH of the purified, substantially pH neutral, crosslinked HA gels are preferably adjusted to cause the gel to become slightly alkaline such that the gels have a pH of greater than about 7.2, for example, about 7.5 to about 8.0. This step may be accomplished by any suitable means, for example, by adding a suitable amount of dilute NaOH, KOH, $NaHCO_2$ or LiOH, to the gels or any other alkaline molecule, solution and/or buffering composition know by one skilled in the art.

about 400 Pa*s, or about 250 Pa*s to about 400 Pa*s, or about 50 Pa*s to about 250 Pa*s.

After homogenization, the HA/lidocaine compositions are introduced into syringes and sterilized. Syringes useful according to the present description include any syringe known in the art capable of delivering viscous dermal filler compositions. The syringes generally have an internal volume of about 0.4 mL to about 3 mL, more preferably between about 0.5 mL and about 1.5 mL or between about 0.8 mL and about 2.5 mL. This internal volume is associated with an internal diameter of the syringe which plays a key role in the extrusion force needed to inject high viscosity dermal filler compositions. The internal diameters are generally about 4 mm to about 9 mm, more preferably from about 4.5 mm to about 6.5 mm or from about 4.5 mm to about 8.8 mm. Further, the extrusion force needed to deliver the HA/lidocaine compositions from the syringe is dependent on the needle gauge. The gauges of needles used generally include gauges between about 18G and about 40G, more preferably about 25G to about 33G or from about 16G to about 25G. A person of ordinary skill in the art can determine the correct syringe dimensions and needle gauge required to arrive at a particular extrusion force requirement.

The extrusion forces displayed by the HA/lidocaine compositions described herein using the needle dimensions described above are at an injection speeds that are comfortable to a patient. Comfortable to a patient is used to define a rate of injection that does not injure or cause excess pain to a

The degree of crosslinking in the HA component of the present compositions is at least about 2% and is up to about 20%.

Source: ‘475 patent, 9:31-33

Use of Present Invention/Composition Limits Claim Scope

"Moreover, when the preferred embodiment is described in the specification as the invention itself, the claims are not necessarily entitled to a scope broader than that embodiment. . . . Here, the specification frequently describes an 'intraluminal graft' as 'the present invention' or 'this invention,' indicating an intent to limit the invention to intraluminal devices."

Edwards Lifesciences LLC v. Cook Inc., 582 F.3d 1322, 1330 (Fed. Cir. 2009)

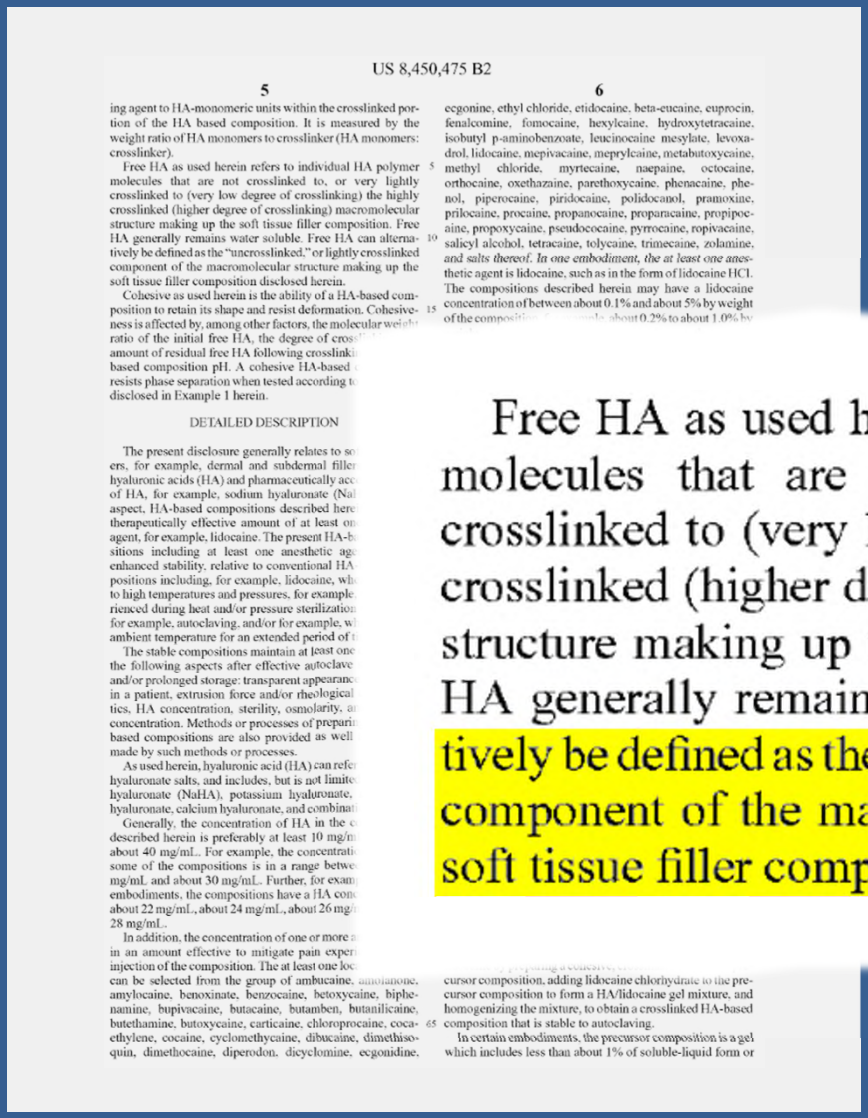
"[T]he written description refers to the fuel filter as 'this invention' or 'the present invention' . . . The public is entitled to take the patentee at his word and the word was that the invention is a fuel filter."

Honeywell Int'l, Inc. v. ITT Indus., Inc., 452 F.3d 1312, 1318 (Fed. Cir. 2006)

"That language clearly defines 'the present invention' [as a particular subset of salts]. . . . Those statements clearly confine the invention to the six identified cations, disclaiming anything else. . . . By conspicuously choosing only certain members of the class, and using the language it did, AstraZeneca conveyed a clear and definitive meaning that it was disclaiming other members of the class."

*Astrazeneca AB v. Hanmi USA, Inc., No. 2013-1490, 2013 U.S. App. LEXIS 25199, *8-9 (Fed. Cir. Dec. 19, 2013)*

‘475 Patent, Lebreton



US 8,450,475 B2

5

ing agent to HA-monomeric units within the crosslinked portion of the HA based composition. It is measured by the weight ratio of HA monomers to crosslinker (HA monomers: crosslinker).

Free HA as used herein refers to individual HA polymer molecules that are not crosslinked to, or very lightly crosslinked to (very low degree of crosslinking) the highly crosslinked (higher degree of crosslinking) macromolecular structure making up the soft tissue filler composition. Free HA generally remains water soluble. Free HA can alternatively be defined as the "uncrosslinked," or lightly crosslinked component of the macromolecular structure making up the soft tissue filler composition disclosed herein.

Cohesive as used herein is the ability of a HA-based composition to retain its shape and resist deformation. Cohesiveness is affected by, among other factors, the molecular weight ratio of the initial free HA, the degree of cross
amount of residual free HA following crosslink
based composition pH. A cohesive HA-based
resists phase separation when tested according t
disclosed in Example 1 herein.

DETAILED DESCRIPTION

The present disclosure generally relates to so
ers, for example, dermal and subdermal filler
hyaluronic acids (HA) and pharmaceutically acc
of HA, for example, sodium hyaluronate (Na
aspect, HA-based compositions described here
therapeutically effective amount of at least on
agent, for example, lidocaine. The present HA-b
sitions including at least one anesthetic ag
enhanced stability, relative to conventional HA
positions including, for example, lidocaine, wh
to high temperatures and pressures, for example
rienced during heat and/or pressure sterilization
for example, autoclaving, and/or for example, w
ambient temperature for an extended period of t

The stable compositions maintain at least one
the following aspects after effective autoclave
and/or prolonged storage: transparent appearanc
in a patient, extrusion force and/or rheological
tics, HA concentration, sterility, osmolarity, a
concentration. Methods or processes of prepari
based compositions are also provided as well
made by such methods or processes.

As used herein, hyaluronic acid (HA) can refe
hyaluronate salts, and includes, but is not limite
hyaluronate (NaHA), potassium hyaluronate,
hyaluronate, calcium hyaluronate, and combinat

Generally, the concentration of HA in the c
described herein is preferably at least 10 mg/m
about 40 mg/mL. For example, the concentrati
some of the compositions is in a range betwe
mg/mL and about 30 mg/mL. Further, for exam
embodiments, the compositions have a HA con
about 22 mg/mL, about 24 mg/mL, about 26 mg/
28 mg/mL.

In addition, the concentration of one or more a
in an amount effective to mitigate pain exper
injection of the composition. The at least one loc
can be selected from the group of ambucaine, amolanone,
amylocaine, benoxinate, benzocaine, betoxycaine, biphe-
namine, bupivacaine, butacaine, butamben, butanilicaine,
butethamine, butoxycaine, carticaine, chloroprocaine, coca-
ethylene, cocaine, cyclomethycaine, dibucaine, dimethiso-
quin, dimethocaine, diperodon, dicyclomine, ecgonidine,

6

ecgonine, ethyl chloride, etidocaine, beta-eucaine, euprocin, fenalcomine, fomocaine, hexylcaine, hydroxytetracaine, isobutyl p-aminobenzoate, leucinocaine mesylate, levoxadrol, lidocaine, mepivacaine, meprylcaine, metabutoxycaine, methyl chloride, myrtecaine, naepaine, octocaine, orthocaine, oxethazaine, parethoxycaine, phenacaine, phenol, piperocaine, piridocaine, polidocanol, pramoxine, prilocaine, procaine, propanocaine, proparacaine, propipocaine, propoxycaine, pseudococaine, pyrrocaine, ropivacaine, salicyl alcohol, tetracaine, tolycaine, trimecaine, zolamine, *and salts thereof. In one embodiment, the at least one anesthetic agent is lidocaine, such as in the form of lidocaine HCl.*

The compositions described herein may have a lidocaine concentration of between about 0.1% and about 5% by weight of the composi about 0.2% to about 1.0% by

cursor composition, adding lidocaine chlorhydrate to the precursor composition to form a HA/lidocaine gel mixture, and homogenizing the mixture, to obtain a crosslinked HA-based composition that is stable to autoclaving.

In certain embodiments, the precursor composition is a gel which includes less than about 1% of soluble-liquid form or

Free HA as used herein refers to individual HA polymer molecules that are not crosslinked to, or very lightly crosslinked to (very low degree of crosslinking) the highly crosslinked (higher degree of crosslinking) macromolecular structure making up the soft tissue filler composition. Free HA generally remains water soluble. Free HA can alternatively be defined as the “uncrosslinked,” or lightly crosslinked component of the macromolecular structure making up the soft tissue filler composition disclosed herein.

Source: ‘475 patent, 5:5-13